REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 1, 4, 7-8, and 20-23, the claims currently under examination in this application. Claims 5-6 and 9-19 are canceled. Claims 1 and 8 are amended. Claims 20-23 are added. No new matter is added

Claim 1 has been amended to clarify that the claimed method is a method of diagnosing a human individual's predisposition to an atopic immunological disorder, the method including analyzing the individual for the presence of at least one TIM-1 polymorphism by contacting a biological sample including nucleic acids from an individual with a probe that specifically binds under stringent conditions to the nucleic acid sequence of a TIM-1 allele, where the presence of the polymorphism is indicative of an individual's predisposition to develop an atopic immunological disorder. Support for this amendment can be found in the specification on page 3, paragraph 21 and page 11, paragraph 44 as exemplary locations.

Claim 8 has been amended for clarity to indicate that HAV seropositivity in an individual expressing an allele of TIM-1 which includes the amino acid sequence MTTTVP, SEQ ID NO:25, residues 158-163 is indicative of a reduced risk of developing atopy, as requested by the Examiner. Support for this amendment can be found in the specification on page 2, paragraph 6 as an exemplary location.

Claims 20 and 21 have been added. Support for Claim 20 can be found in the original Claim 1 and in the specification on page 3, paragraph 21; page 10, paragraphs 40-42 and page 11, paragraph 44. Support for Claim 21 can be found in the original Claim 1 and in the specification on page 8, paragraph 37, page 10, paragraphs 40-42 and page 11, paragraph 44.

As no new matter has been added by way of these amendments, entry thereof by the Examiner is respectfully requested.

Applicants note the withdrawal of Claims 2-3, and respectfully submit that if a linking claim is found to be patentable, rejoinder of Claims 2-3 is appropriate. Applicants also confirm the election of SEQ ID NO:25 for the examination of group I, claims 2-4. Applicants respectfully submit, however, that it is proper to examine the invention with respect to all of the polymorphisms of the human TIM-1 gene.

Applicants have amended the specification to comply with all sequence rules. The Sequence Listing appended herewith replaces any previously filed Sequence Listings of the subject application.

Claim Rejections – 35 USC § 112, 2nd paragraph

Claim 8 is rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, Examiner states that it is unclear how "analyzing said individuals for the presence of hepatitis A seropositivity" is used in determining predisposition to an immunological disorder, and vague as to how it limits a diagnosis performed by detecting a polymorphism in TIM-1.

Applicants have amended the indefinite language of Claim 8 to clarify that HAV seropositivity in an individual expressing an allele of TIM-1 which includes the amino acid sequence MTTTVP, SEQ ID NO:25, residues 158-163 is indicative of a reduced risk of developing atopy. Accordingly, the withdrawal of this rejection is respectfully requested.

Claim Rejections – 35 USC § 112, 1st paragraph - Enablement

Claims 1, 4 and 7-9 have been rejected under 35 USC §112, first paragraph, for not enabling any person skilled in the art to make and use the invention. Specifically, the Office Action asserts that while the specification is enabling for a method for determining a Caucasian's predisposition to atopy protection by detecting the presence of the homozygous polymorphism of 157insMTTTVP of TIM-1 in a hepatitis virus A positive Caucasian individual, wherein the presence of the MTTTVP insertion is indicative of a Caucasian's predisposition to be protected against atopy, it is not enabling for a method for diagnosing any human or non-human individual's predisposition to any immunological disorder by analyzing for the presence of any TIM-1 polymorphism.

The claims as amended recite a method of diagnosing a human individual's predisposition to an atopic immunological disorder, the method including analyzing the individual for the presence of at least one TIM-1 polymorphism by contacting a biological sample comprising nucleic acids from the individual with a probe that specifically binds under stringent conditions to the nucleic acid sequence of a TIM-1 allele, where the presence of the

polymorphism is indicative of an individual's predisposition to develop an atopic immunological disorder.

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."[1]

To comply with 35 U.S.C. § 112, first paragraph, a specification need only enable a skilled artisan to make and use the claimed invention without undue experimentation. Accordingly, a specification complies with the statute even if a reasonable amount of experimentation is required, as long as the experimentation is not "undue". As reviewed in the Office Action, one way to determine if undue experimentation is required is to analyze the subject specification in light of the *Wands* factors:[2] (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the predictability or unpredictability of the art, (5) the quantity of experimentation necessary, (6) the relative skill of those in the art, (7) the amount of direction or guidance presented, and (8) the presence or absence of working examples. However, all of the factors need not be reviewed when determining whether a disclosure is enabling.[3]

Applicants respectfully submit that, when evaluated in view of the relevant *Wands* factors, the specification clearly enables one of skill in the art to practice the subject invention without undue experimentation. In other words, Claims 1, 4 and 7-9 recite subject matter that is adequately described in the specification in such a way as to teach a skilled artisan how to make and use the claimed invention without having to practice undue experimentation. The relevant enablement factors cited in the Office Action are discussed in detail below.

The nature of the invention and the breadth of the claims

The claims as amended are drawn to a method of diagnosing a human individual's predisposition to an atopic immunological disorder, the method including analyzing the individual for the presence of at least one TIM-1 polymorphism, where the presence of the

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[1] *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

[2] *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988)

[3] See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991).

polymorphism is indicative of an individual's predisposition to develop an atopic immunological disorder.

The amended claims of the instant application encompass the analysis of human individuals specifically. The amended claims encompass the diagnosis of predisposition to atopic immunological disorders specifically. The amended claims encompass analysis for the presence of a polymorphism within the TIM-1 open reading frame or within regulatory sequences which immediately flank it. In other words, in order to fall within a claim, a polymorphism must be restricted to the TIM-1 gene with its attendant chromosomal location, consensus sequence, and structural features. *Thus, the claim language excludes any sequences which are not so restricted.*

Guidance in the specification and working examples

Applicants respectfully submit that the specification, coupled with the information known in the art, would enable one of skill in the art to use the invention without undue experimentation. Relevant enablement factors are discussed in detail below.

The instant specification describes atopic conditions the diagnosis of which are of interest according to the claimed method, including asthma, allergic rhinitis (hay fever), atopic dermatitis (eczema) and food allergies. The specification also names allergens commonly associated with atopic immunological disorders. The specification describes the TIM gene family, provides its chromosomal location, sequence organization and sequences of commonly occurring human alleles. Page 9 of the specification incorporates by reference numerous publications linking the TIM gene family to a wide spectrum of immune-mediated diseases including diabetes, inflammatory bowel disease, atopy, asthma and autoimmune thyroiditis. The molecular characteristics of the TIM gene products are discussed in detail, including important sequence motifs and structural features as well as expression pattern in various tissues. Also provided is a discussion of methods of isolating TIM genes from tissue samples, which methods are known to the art. A review, with references, of techniques for genotyping TIM alleles for the purpose of diagnosis is provided, including the preparation of cDNA, array assays, the use of antibodies, the use of various labels and other methods known to the art.

Accordingly, the specification provides everything that is needed such that the ordinarily skilled artisan can identify polymorphic allelic variants of TIM-1 associated with atopic conditions and employ such polymorphisms for diagnostic purposes.

Compliance with the enablement requirement under Section 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.[4] Furthermore, "Nothing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."[5]

Nonetheless, Example 6 demonstrates experimental reduction to practice of the claimed method. In Example 6, a clinically identified population of patients including both HAV seropositive and seronegative individuals suffering from atopic disorders were genotyped with respect to their TIM-1 alleles. Commercially available software analysis of the genotypes revealed a statistically significant association of protection from atopy with the 157insMTTTVP allele in HAV seropositive subjects. As such, this combination of insertion allele and HAV seropositivity holds predictive value for predisposition to atopy for any individual in the group or any other individual having the identified clinical characteristics. Accordingly, an actual working example has been disclosed in the specification.

With regard to diagnosis of an individual's predisposition to an atopic immunological disorder by analyzing the individual for the presence of at least one TIM-1 polymorphism, the Office Action asserts that although the allele determination is routine in the art, the correlation of an allele to any type of immunological disorder or atopy in any human or non-human individual is unpredictable and the specification does not predictably correlate each of these polymorphisms with any type of immunological disorder or atopy in any human or non-human individual.

Applicants respectfully submit that the claims as amended are directed not to diagnosis in of <u>any</u> type of immunological disorder in <u>any</u> human or non-human individual, but to the diagnosis of atopic immunological disorders in human individuals.

The specification supports the diagnosis of predisposition to atopic immunological disorders in humans. As reviewed above, the specification provides techniques known to the art to identify TIM-1 alleles associated with atopic disorders and the means to diagnose predisposition to atopy using those alleles. Example 6, paragraphs 194-208, demonstrates

[4] In re Borkowski, 164 USPQ at 645.
[5] *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).

statistically significant (P=0.0005) interactions between a commonly carried TIM-1 allele and protective status towards atopy in human subjects. As such, the specification both describes and demonstrates means to diagnose a predisposition to atopy in humans by detecting allelic sequences in the TIM-1 gene.

The Office Action asserts that the specification does not predictably correlate a method for diagnosis which determines a predisposition to any type of immunological disorder in any human or non-human by detecting any polymorphism within TIM-1. Applicants respectfully disagree.

Firstly, the claims as amended are directed to atopic immunological disorders specifically.

Secondly, the amended claims encompass a method of analysis for the presence of polymorphisms using a probe that specifically binds under stringent conditions to the nucleic acid sequence of a TIM-1 gene. Applicants respectfully emphasize that the claims are not directed to a product consisting of TIM-1 sequences or probes, but to a method of analyzing and using the same. The pending claims are neither product claims nor product-by-process claims; as such, a specific polymorphic sequence being probed by the instant method constitutes an object of analysis rather than a claimed product. As reviewed above, the structure of the TIM gene family is established in detail in the specification; general methods of preparing probes which bind to specific sequences are robust, commonplace and well known to the art.

Accordingly, the routine clinical identification of a population or subpopulation of individuals suffering from one or more types of atopy identifies a population in which the instant method of analysis finds use. Techniques for generating probes with specificity for any of the TIM-1 alleles found therein are routine in the art, and such probes are generated as a consequence of applying the claimed method.

Moreover, MPEP 2138.05 states that reduction to practice may be an actual reduction or a constructive reduction to practice. The instant specification shows, in multiple experimental examples, unambiguous evidence that the TIM-1 gene is associated with protection from atopy. The constructive reduction to practice constituted by the present application thus provides both a rationale for the selection of the TIM-1 gene as a diagnostic tool for multiple atopic immunological disorders and the means to effect such diagnoses using TIM-1 alleles in clinically identified atopic individuals. Since the instant specification provides: atopic conditions of interest to the claimed method, a detailed description of the TIM gene family including its chromosomal

location and sequence content, molecular characteristics of the TIM gene products including sequence motifs and structural features, numerous referenced publications linking the TIM gene family to multiple immune-mediated diseases, description of the important role of the TIM-1 gene in immunological responses, methods of isolating TIM genes from tissue samples, techniques for genotyping TIM alleles for the purpose of diagnosis, and typical methods of preparing and detecting probes, the specification provides everything that is needed such that the ordinarily skilled artisan can identify polymorphic allelic variants of TIM-1 associated with atopic conditions and use such polymorphisms for diagnostic purposes by employing straightforward techniques known to the art. Accordingly, the specification amply supports a constructive reduction to practice for any TIM-1 allele by the present application.

The Office Action asserts that tables S3 and S4 demonstrate that 157insMTTTVP is predictably correlative for only the Caucasian population that is HAV positive and homozygous for the allele and that neither the HAV negative or HAV positive population of Asian subjects is statistically relevant to diagnose a predisposition to any immunological disorder or atopy.

Applicants respectfully submit that this is incorrect. In both tables, consisting of subgroup analyses for Caucasian and Asian populations, the "157insMTTTVP 1,2 vs 0 alleles" column reports a significant P value for HAV+ individuals, P=0.024 and P=0.036, respectively. As such, the 157insMTTTVP allele is predictably correlative for the group including seropositive heterozygous and homozygous individuals in both Caucasian and Asian populations. It is unclear why the Office Action states that this is not "statistically relevant" data. Further, the lack of presentation of a subgroup analysis of African American individuals is due solely to the small n value of the group (specification, paragraph 202). Since the analysis according to Table 1 was performed using a Cochran-Mantel-Haenszel chi-square test with racial stratification (specification, paragraph 199), the statistical conclusion therein is valid for all included ethnicities.

The Office Action enumerates various aspects of the specification which are asserted to be unclear. Applicants sincerely believe these queries have been addressed by the above response.

The Office Action states that the specification appears to be conceiving of possible scenarios where the presence of any polymorphism in TIM-1 would indicate the presence - or absence - of any immunological disorder. Applicants respectfully disagree. The specification teaches the use of a polymorphism in TIM-1 to determine a statistical likelihood (i.e.

predisposition) of vulnerability to an atopic immunological disorder, not the presence or absence thereof. It is nowhere recited or implied in the instant Application that every polymorphism of TIM-1 will carry predictive association with an atopic disease. The claimed method relies on techniques well known to the art in order to assay statistical association of any given polymorphism with an atopy predisposition.

The Office Action further asserts that it is unclear how one of skill in the art would determine which polymorphism of the TIM-1 gene would diagnose atopy. Applicants again respectfully disagree. As discussed, populations of individuals suffering atopic conditions are routinely clinically identifiable. Given the specification, in which the important role of the TIM-1 gene in immunological responses and atopic disorders is described and diagnostic conditions exemplified, coupled with the information known in the art, it would be no more than a matter of routine for one of skill to associate a polymorphism in TIM-1 with an atopic condition of interest and employ the claimed method to diagnose a predisposition to the atopic condition of interest.

The unpredictability of the art, the state of the prior art, and the level of skill in the art

In making this rejection, the Examiner asserts that the level of unpredictability in associating a particular polymorphism with a phenotype is high. The Examiner asserts that because the art is unpredictable, one cannot reliably associate any TIM-1 polymorphism with an atopic disorder. Applicants respectfully disagree.

The Examiner asserts that it is unpredictable as to whether any polymorphism, including the specifically claimed polymorphic positions would be associated with atopy or immunological disorders in any other non-human organism.

Applicants respectfully submit that the claims as amended are directed to the diagnosis of atopic immunological disorders in human individuals. As such, Applicants sincerely believe this concern to have been addressed.

The Examiner presents a GeneCard analysis indicating 135 SNPs in the TIM-1 gene, asserting that the specification does not teach any association of these 135 polymorphisms with any type of immunological disorder or atopy.

As discussed above, techniques for generating probes with specificity for any of the TIM-1 SNPs are routine in the art, and such probes are generated by straightforward techniques as a consequence of applying the claimed method.

The Examiner refers to Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) as

post filing art which teaches that since disease conditions can be multigenic and etiologies population-dependent, that genetic tests should be evaluated in terms of their detection of:

1) a particular genetic variant;

2) for a particular disease;

3) in a particular population; and

4) for a particular purpose (Kroese et al., page 477).

Applicants respectfully submit that the presently claimed method fulfills each of these conditions.

1) The method as claimed teaches the detection of polymorphic sequences at a particular, well-defined genetic locus using probes for specific sequences;

2) atopic disorders are well-defined and routinely clinically reported;

3) the populations studied by the claimed method are clinically definable by the presence of disease; and

4) the specific purpose of the method as claimed, diagnosing a predisposition to atopic immunological disorders, plays to the strengths of genetic analysis precisely because the goal is association of an allele with a likelihood of disease. While discovery of the mechanistic etiology of the disease is desirable, and likely in the case of TIM-1, it is not prerequisite for the effectiveness of the method as claimed.

The Examiner states that Kroese et al. further suggest that all measures of test performance be presented with their 95% confidence intervals. Applicants submit that he major finding of the exemplified reduction to practice, the association of protection from atopy with the 157insMTTTVP allele in the presence of HAV seropositivity, is presented with P values representing >95% confidence. HAV+ individuals with 1 or 2, 2, or a single 157insMTTTVP allele are protected from atopy at P=0.0005, P=0.002, and P=0.004, respectively (Table 1). The critical findings of the analyses presented in Tables S2 through S4 likewise meet this standard. As such, the recommendations of Kroese et al. are satisfied by the present Example.

The Examiner refers to Lucentini (The Scientist, 2004, Vol 18, page 20) as post-filing art which states that it is common for follow-up studies to find gene-disease associations wrong. Applicants note that the Lucentini in the second column, first full paragraph presents recommendations for avoiding this error:

1) accounting for "prior probability", a subjective but reasonable measure of how plausible the gene-disease association in question looked prior to the study; and

2) large enough sample size to avoid a cofounder population stratification effect.

Applicants respectfully submit that the presently claimed method fulfills both of these conditions:

1) As reviewed above, the importance of the TIM-1 gene family is described in the specification, which includes numerous referenced publications linking the TIM genes to multiple immune-mediated diseases and description of the important role of the receptor encoded by the TIM-1 gene in immunological responses. The specification further states in the introduction to Example 6, page 53, paragraph 193:

"TIM-1 is expressed by activated CD4 T cells during the development of helper T cell (Th2) responses and appears to regulate cytokine production. Therefore, we postulated that HAV interaction with TIM-1 on lymphocytes could modify T cells in a manner that protects against atopy, and that polymorphisms in TIM-1 might alter susceptibility to atopy."

The introduction further states:

"By sequencing lymphocyte cDNA, we identified a six amino acid insertion, 157insMTTTVP. 157insMTTTVP is located at the center of an extracellular mucin-like region that is required for efficient HAV uncoating, and because 157insMTTTVP lengthens this critical region by 12-14%, this variation may impact the efficiency of viral entry."

As such, the prior probability of gene-disease association was reasonably considered to be high in the course of designing the experiment.

2) The population stratification effect results from the tendency of populations to carry high frequencies of both certain genes and certain diseases owing to common ancestry. As reviewed above, the purpose of the method as claimed is diagnosis of a predisposition to atopic immunological disorders, not discovery of a causal link of polymorphism to disease. While discovery of the mechanistic etiology of the disease is desirable, and likely in the case of TIM-1, it is not prerequisite for the effectiveness of the method as claimed; genetic linkage alone is sufficient. Moreover, since the population displaying displaying atopic conditions is large and diverse as evidenced in the present specification, the likelihood of founder effects is small, and the likelihood of such effects reducing the informativity of the data in a study comprising multiple ethnic groups is smaller.

Accordingly, the recommendations of Lucentini are satisfied with respect to the instant Application, substantiating the reliability of the exemplified results.

The Examiner refers to Noguchi et al. (Genes and Immunity (2003) 4: 170-173) as

teaching a lack of association between polymorphisms in the TIM-1 gene and asthma in Japanese asthmatic families.

Applicants firstly note that none of the polymorphisms identified by Noguchi et al. were associated with asthma in the present experimental examples (specification, Example 6; Noguchi et al., page 170, right column, second full paragraph).

Applicants secondly note that the instant Example 6 was practiced upon individuals answering to calls for allergic reactions and responding positively for allergic rhinitis, atopic dermatitis and food allergy, and positive for specific IgE against local allergens, not for familial asthma (specification, page 57, paragraph 201). As such, there is no apparent contradiction between the results of Noguchi et al. and those of the present example.

Moreover, Applicants emphasize that it is nowhere recited or implied in the instant Application that every polymorphism of TIM-1 must carry predictive association with an atopic disease. The claimed method relies on techniques well known to the art in order to assess statistical association of any given polymorphism with an atopy predisposition.

The Examiner refers to Applicants' own post-filing art, Umetsu et al. (Ann NY Acad Sci, 2004, 1029:88-93), as teaching results which are confirmatory of those presented in the instant Application, namely, that serotype HAV+ insertion allele carriers are protected against atopy while HAV- carriers are not. As such, there is no apparent contradiction between the result of Umetsu et al. and those of the present examples.

Applicants emphasize that it is nowhere recited or implied in the instant Application that every polymorphism of TIM-1 will carry association with an atopic disease in the absence of any other infectious agent or associated gene. Applicants submit that there is no *a priori* reason that viral infection should be excluded from the characteristics of an individual suffering from atopy in whom the method finds use.

The Examiner refers to Graves et al. (J Allerg Clin Immun01 2005, vol 1 18, pages 650-656) as post-filing art reporting a study in which TIM family polymorphisms were assessed for multiple atopic condition in children of multiple ethnicities, finding that some alleles of TIM-1 displayed statistically significant association with atopy and some did not. One deletion polymorphism in exon 4 was found to be associated with atopy, multiple point mutants were not (Graves et al., i.e. abstract).

Applicants firstly note that none of the polymorphisms identified as not significantly associated with atopy by Graves et al. were found to be associated with atopy in the present

experimental examples (specification, Example 6; Graves et al., page 170, right column, second full paragraph).

Moreover, Applicants emphasize that it is nowhere recited or implied in the instant Application that every polymorphism of TIM-1 must carry predictive association with an atopic disease. The claimed method relies on techniques well known to the art in order to assess statistical association of any given polymorphism with an atopy predisposition.

As such, there is no apparent contradiction, and indeed, given the differing polymorphisms assessed, there is significant consonance between the results of Graves et al. and those of the present example. Graves et al. find that multiple alleles show statistically significant association with atopic conditions (Graves et al., page 652, right column, second full paragraph). Graves et al. teach that these "associations were strong enough to remain significant after adjustment for multiple comparisons" (transition paragraph from page 653-654). Contra the Examiner, Graves et al. teach that although a limitation of the analysis is reflected in the ethnic heterogeneity of the Tucson population, similar results were replicated in children with two Caucasian parents, indicating that the significant associations are unlikely to be related to population stratification as the result of ethnicity (page 655, right column, third full paragraph). Accordingly, the study does not cast doubt upon but rather substantiates the rationale and feasibility of the claimed method.

Further in support of enablement of the claimed method with regard to African Americans, Gao et al. (J Allergy Clin Immunol. 2005 May;115(5):982-8) is appended herewith as Exhibit A.

Gao et al. report that genetic variants of the TIM-1 gene contribute to asthma susceptibility in the African-American population. In Gao et al., frequencies of the TT genotype for a single nucleotide polymorphism rs2277025 and a homozygous deletion variant 157delMTTTVP in the fourth exon of the TIM-1 gene were higher among patients with patients with asthma compared with controls (odds ratio [OR], 2.779, P = .016; and OR, 3.09, P = .022, respectively). The association was further substantiated by haplotype analysis of these and two additional SNPs (OR, 2.48; P = .004), and also by family-based tests for the allele and haplotype carrying 157delMTTTVP (P = .009 and P = .048, respectively). Accordingly, TIM-1 allelic variation has been statistically associated with atopic conditions in an African American population.

One of skill in the art is well-prepared by the instant specification to practice the claimed

method. The relevant ordinarily skilled artisan is generally a skilled laboratory technician with experience in molecular biology and/or a scientist with the equivalent of a doctoral degree in molecular biology techniques. Furthermore, such artisans are required to keep abreast of the latest technology through continuing education and reading of scientific journal articles. As such, the skill level of those developing and using methods for manipulating DNA and performing nucleic acid-based assays is high. It would therefore be straightforward for one of skill in the relevant art to distinguish TIM-1 alleles which are of use in the presently claimed method.

Quantity of Experimentation

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[6]
As the court explained[7]:

"[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

Practitioners in the chemical and molecular biological arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.[8]

The claims recite a method of diagnosing a human individual's predisposition to an atopic immunological disorder, the method including analyzing the individual for the presence of at least one TIM-1 polymorphism by contacting a biological sample including nucleic acids from

[6] See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).
[7] *In re Wands* 8 USPQ 2d at 1404

an individual with a probe that specifically binds under stringent conditions to the nucleic acid sequence of a TIM-1 allele, where the presence of the polymorphism is indicative of an individual's predisposition to develop an atopic immunological disorder.

The only experiments that need be performed to enable the entire scope of the claim are those designed to assess the association of a TIM-1 polymorphism with an atopic condition in a population of interest. The sequence of such a polymorphism is determined through routine experimentation, typically employing nothing more than performing the same assay disclosed in the specification on a clinically defined cohort using polypeptides made by routine, high-throughput sequencing and DNA synthesis techniques. Since these experiments are routine in nature, no undue experimentation is required. In other words, the only experimentation required to enable the claimed invention are experiments to confirm a statistical association of an allele in a population, and since this only requires a routine assay to determine, no undue experimentation is necessary.

In sum, the amount of experimentation required to establish conditions in which detection of a polymorphism in the TIM-1 gene permits the diagnosis of a predisposition to an atopic immunological disorder would not be undue because a) a working example has been provided, b) guidance on how to assess the association has been provided, c) it is straightforward to establish a reasonable correlation between atopy and members of the species within a genus of this breadth, and d) one of skill in the art would be able to perform such screening experiments as a matter of routine.

The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation. Accordingly, Applicants respectfully request withdrawal of the rejection.

Claim Rejections – 35 USC § 112, 1st paragraph – Written Description

Claims 1, 4 and 7-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The rejected claims are alleged to contain subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time of filing, had possession of the claimed invention.

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[8] *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

Specifically, the Office Action asserts that the rejected claims provide no structural limitation regarding what is encompassed by the term "TIM-1 gene." The Office Action further alleges that the claims are broadly drawn to methods comprising the detection of any polymorphic variant of TIM-1 gene that is associated with any type of immunological disorder or atopy. The Office Action alleges that the claims are broadly drawn to a method that encompass a plurality of nucleic acids and an extremely large genus of polymorphic variants of the TIM- 1 gene.

With regard to the definition of "a TIM gene," the specification explicitly states on page 10, paragraph 41, that:

> The term Tim gene shall be intended to mean the open reading frame encoding any one of the specific Tim polypeptides, introns, as well as adjacent 5' and 3' non-coding nucleotide sequences involved in the regulation of expression, up to about 1 kb beyond the coding region, but possibly further in either direction.

With regard to the structural limitations of the TIM-1 gene, Applicants submit that the specification provides ample support for the claims in this regard. Page 45, paragraph 167 of the specification states:

> The cytoplasmic domains of TIM gene family members are the most conserved domain between mouse and human orthologues, e.g., 77% identity between the human and mouse TIM-3 cytoplasmic domains... Each TIM gene contains a distinct predicted tyrosine signaling motif. The cytoplasmic region of TIM-1 contains two tyrosine residues and includes a highly conserved tyrosine kinase phosphorylation motif, RAEDNIY. The expanded region, SRAEDNIYIVEDRP, contains a predicted site for Itk and EGF receptor phosphorylation... The extracellular IgV domain of the TIM proteins also contains a predicted integrin-binding motif that is similar to the SVVYGLR motif of osteopontin that is involved in adhesion via alpha(9)beta(1), alpha(4)beta(1), and alpha(4)beta(7) integrins.

Moreover, Figures 7, 8 and sequence listings 17 through 39 provide ample sequence information, at both the nucleotide and the amino acid level, such that one of skill in the art is

readily able to use standard and convenient techniques such as PCR amplification and high-throughput sequencing in order to arrive at a probe which will specifically bind under stringent conditions to the nucleic acid sequence of any TIM-1 polymorphism encountered in the clinic.

Examiner asserts that the claims are drawn to a large genus of polymorphic alleles encompassing a plurality of nucleic acids.

Applicants respectfully submit that modern array-based methods frequently query thousands of genes, often of unknown sequence. In comparison, the 135 SNP positions reported in the GeneCard cited by Examiner represent a modest degree of variation, and that within a single gene with highly conserved motifs.

Accordingly, upon encountering a TIM-1 polymorphism in a population, one of skill in the art is readily able to envision the necessary structure of probes suitable for use in the claimed method. The structure of the TIM gene family is established in detail in the specification, and generalizable methods of preparing probes which bind to specific sequences are robust, commonplace and well known to the art. Accordingly, techniques for generating probes with specificity for any of the TIM-1 alleles found therein are routine in the art, and such probes are therefore routinely generated in the course of applying the claimed method.

As reviewed above, the amended claims encompass a method of analysis for the presence of polymorphisms using a probe that specifically binds under stringent conditions to the nucleic acid sequence of a TIM-1 gene. The claims are not directed to products consisting of TIM-1 sequences or probes; as such, a specific polymorphic sequence being probed by the instant method constitutes an object of analysis rather than a claimed product.

Applicants therefore submit that, as stated on page 11, paragraph 40 of the specification, "The exact composition of the primer sequences is not critical to the invention, but for most applications the primers will hybridize to the subject sequence under stringent conditions, as known in the art." Since the level of skill in the art regarding determination of allelic sequence is very high, absolute foreknowledge of the polymorphic TIM-1 sequences, and thus probe composition, is not relevant or required in order to use the method as claimed. Accordingly, the requirement of such foreknowledge is not the correct standard for examining the claimed method.

While there may be sequences within the genus defined by "TIM-1 polymorphism" which will not significantly associate with atopic immunological conditions, the courts have clearly taught that even in unpredictable arts the specification does not have to disclose every species

of a genus that would work and every species that would not work. The court has very clearly explained[9]:

"To require such a complete disclosure would apparently necessitate a patent application or applications with thousands of catalysts....More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid literal infringement of such claims by merely finding another analogous catalyst complex which could be used ...."

The claims of the instant application encompass a method of diagnosing a human individual's predisposition to an atopic immunological disorder which includes analyzing the individual for the presence of at least one TIM-1 polymorphism by contacting a biological sample including nucleic acids from an individual with a probe that specifically binds under stringent conditions to the nucleic acid sequence of a TIM-1 allele, where the presence of the polymorphism is indicative of an individual's predisposition to develop an atopic immunological disorder. Since one of skill in the art would recognize that a reasonable correlation is readily established by known methods between atopy and members of this genus, and since every species in a genus does not have to be tested for the genus to be enabled, extensive, per-sequence disclosure or guidance regarding the active species in the genus does not have to be provided in order for a genus of this scope to be enabled.

Applicants respectfully request withdrawal of the rejection.

[9] *In re Angstadt*, 190 USPQ 214, at 219 (CCPA 1976)

CONCLUSION

In view of the amendments and remarks above, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issuance.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-235CIP.

Respectfully submitted,

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